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Lecture 1

Smoking and Smoking Cessation

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The tobacco plant, which is native to North America, has developed a chemical defense against insect predators(1). The plant commits a significant amount of metabolic energy synthesizing the neurotoxin nicotine. This compound affords the tobacco plant some protection against insect predations. Interestingly, a 20% solution of nicotine was, at one time, a commercially successful insecticide.

Nicotine is active not only on the insect nerve system but also on the mammalian nervous system (2–6). In this regard, nicotine is active on a subset of acetylcholine receptors, the so-called nicotinic receptors. Through actions on these receptors, nicotine can activate diverse pathways within the central nervous system. Activation of these pathways can cause a number of pleasant effects, including a sensation of euphoria. In a study of drug experienced volunteers, Henningfield and colleagues observed that nicotine, cocaine, amphetamine and morphine all resulted in a similar degree of euphoria(7). Nicotine, however, was about 10-fold more active on a concentration basis. The pleasant sensation associated with nicotine is, undoubtedly, one of the important reasons why many individuals choose to smoke. This effect of smoking was well known to ancient Americans who had established trade in both tobacco and in the equipment required to smoke it centuries before the European discovery of the North American continent.

Nicotine is associated with other central nervous system effects in addition to causing euphoria. A number of studies have demonstrated that nicotine can improve cognitive function, particularly tasks requiring memory and attention(8–10). Nicotine can also affect mood and may do so by causing inhibition of monoamine oxidase(11). In this respect, cigarette smoking may have an effect similar to antidepressant doses of monoamine oxidase inhibitors. Nicotine can also affect nicotine receptors. Administration of nicotine to animals results in a significant increase in nicotine receptor number(12–14). Such an effect may contribute to the addictive potential of nicotine. Finally, nicotine induces alterations in both appetite and metabolism through mechanisms which are poorly understood. These effects, however, consistently cause a small but significant decrease in body weight.

The verious central nervous system effects of nicotine are also associated with addiction(2, 15, 16).

Table 1 Nicotine Withdrawal Symptoms (DSM-IV)

Dysphoric or depressed mood
Insomnia
Irritability, frustration or anger
Anxiety
Difficulty concentrating
Restlessness
Decreased heart rate
Increased appetite or weight gain

Acute withdrawal from nicotine results in a well defined syndrome (Table 1)(17). In addition to these symptoms, craving for smoking and drug-seeking behavior are other manifestations of acute nicotine withdrawal. Despite its addictive potential, it is unlikely that cigarette smoking would be regarded as the major public health it is if it were not for the associated health risks. In this regard, cigarette smoking is the major preventable cause of mortality in the United States(1). It is likely that excess mortality due to cigarette smoking will become increasingly important in the developing world as cohorts of smokers accumulate a sufficient number of pack years of smoking.

Lung disease due to cigarette smoking develops insidiously. As shown initially by Fletcher and Peto and subsequently confirmed, lung functions increase into young adulthood(18). In normal individuals, lung function then declines slowly with a loss of 10–20 ml of FEV_1 annually, or a loss of approximately one liter in a 50-year adult life span. The average smoker loses lung function at approximately twice this rate. Some smokers, however, lose function at an accelerated rate such that lung function eventually declines below 50% of predicted. At these levels, symptoms related to reduced lung function can be menifested(19). Thus, symptomatic COPD often develops in the sixth decade of life. It is correct, however, to recognize this as a late manifestation of cigarette smoking, a disease which often begins in childhood.

Most people who begin smoking do so during adolescence(20–22). In the United States, individuals who have not started smoking by age 25 are unlikely to do so(23). These demographics for smoking initiation are well known to the tobacco industry. It is in order to target potential customers that advertising campaigns such as the "old Joe Camel" campaign were designed. Such campaigns can be exceedingly effective at creating recognition for products(24). In Japan, distribution of free cigarettes may have a similar effect in helping potential smokers begin a life-long addiction.

Smoking is obviously a complex social phenomenon. Regulating tobacco use through social means is a legitimate exercise of public policy. While results are controversial(25), some studies suggest that restriction of sales of tobacco to minors can decrease use of cigarettes among adolescents(26). Similarly, increasing the price through taxation can both decrease cigarette use and likely decrease initiation(27, 28). Prevention of smoking, therefore, is a legitimate public health goal.

Failing prevention, helping the addicted smoker quit represents an important medical goal. There are several approaches to achieve this goal. These include behavioral approaches as well as pharmacological treatments. Options to help reduce the health risks of smokers who cannot quit are currently under investigation. The following discussion will provide a brief overview of these smoking cessation modalities. Datailed reviews are available elsewhere.

A variety of behavioral strategies have been developed to help smokers quit(1, 29–31). These approaches help smokers recognize that they will lose a pleasurable activity, often one which is well integrated into their activities of daily living and may be an important means by which they cope with routine life stresses. Behavioral approaches can also help smokers identify high risk situations where relapse is likely. While a variety of approaches have been developed, quit rates for behavioral strategies generally approach 20% abstinence at one year, at least among highly motivated smokers(32). There does appear to be increasing benefit in programs with multiple sessions up to between two to seven sessions and for sessions of up to 10 minutes in length(31).

Two pharmacological approaches have been demonstrated to aid with smoking cessation. The first is nicotine replacement(2, 33, 34). In this regard, the pharmacokinetics of nicotine administration is important to understand. The psychoactive effects of nicotine depend not only on the level of nicotine at the receptors in the central nervous system, but also on the rate of rise in nicotine concentrations. Smoking, therefore, is a particularly effective means at delivering nicotine in order to achieve its psychopharmacological effects. That is, nicotine which is highly lipid soluble and volatile, is rapidly absorbed across the alveolar surface into the pulmonary capillary and hence arterial blood. Blood nicotine levels rise exceedingly rapidly after inhaling cigarette smoke. After smoking, nicotine levels fall,

Table 2 PHARMACOKINETICS OF NICOTINE DELIVERY
adapted from multiple sources including Schneider et al. Clin Pharm. 1 : 65, 1996

	time to max (minutes)	steady state level (ng/ml)
patch	500	20
gum	30	20
inhaler	30	7
nasal spray	10	20
cigarette	10	40

initially through redistribution and subsequently through metabolism. Current concepts suggest that withdrawal symptoms develop when nicotine levels fall below a certain threshold. The concept behind nicotine replacement is to provide adequate nicotine to prevent withdrawal symptoms by a means which avoids the "peaks" associated with the psychoactive "hits." This allows the smoker the opportunity to deal with the behavioral aspects of becoming an non-smoker while reducing the intensity of withdrawal symptoms. Complete freedom from nicotine can then be achieved by discontinuing the nicotine replacement therapy.

The four formulations of nicotine replacement currently available in the United States differ in their pharmacokinetics (Table 2). Blood levels with the multiple dosing formulations are, obviously, dependent on the number of doses administered. Interestingly, all the currently available formulations of nicotine replacement result in approximately a doubling in quit rates over that of placebo when these are combined with a behavioral program(35). The possibility obviously exists for administration of nicotine through combined modalities. It may be that such administration may improve quit rates in selected individuals(36, 37).

Because nicotine is known to activate structures in the dopaminergic pathways of the mesolymbic system, it is interesting that the anti-depressant bupropion which is also active in these pathways has effects on cigarette smoking(38). Clinical trials have demonstrated a significant improvement in smoking cassation rates when bupropion was administered either alone(38) or in combination with nicotine replacement (submitted). Interestingly, the combination appears to result in higher short-term quit rates than either agent alone.

While currently available smoking cessation techniques can help a significant number of smokers to quit, it is estimated that only 30% of smokers will quit before the age of 60(39). Whether reducing smoking either with or without the aid of partial nicotine replacement or whether the use of alternative nicotine delivery systems which are not associated with the high levels of toxins found in cigarette smoke will be beneficial for these individuals remains to be seen. While currently available data are limited, reduction in smoking achieved with concurrent administration of nicotine via nicotine gum has been associated with reduced airway inflammation assessed by bronchoscopy and bronchoalveolar lavage(40). Cigarettes which heat tobacco rather than burning it may be another means to achieve reduction in toxin exposure(41).

Whether such approaches will be beneficial or not is a complex question. Even if there is a reduction in inflammation in the smoker who uses such strategies, the availability of an alternative to complete cessation may decrease overall quit rates. Perhaps more concerning, the availability of a perceived safer way to smoke might increase smoking initiation rates. Either of these two possibilities could have an adverse overall effect on public health. Whether such strategies will have potential benefit and, if so, how they should be regulated and administered will, undoubtedly, pose a number of important medical and social questions.

In summary, cigarette smoking is currently the major preventable cause of mortality in the United

States. It is rapidly achieving a similar notoriety in the developing world. Efforts to prevent smoking initiation can help stem the tide in the epidemic of cigarette smoking related disease. For smokers already addicted, currently available methods to aid in cessation including behavioral and pharmacological approaches can be of significant benefit. Alternative strategies for smokers unable to quit are needed and are under investigation.

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